Detrusor contraction during rapid bladder filling: Caused by cold or warm water? A randomized controlled double-blind trial

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Abstract: PURPOSE: We investigated if the detrusor contraction during rapid bladder filling is provoked by cold or warm water. PATIENTS METHODS: Patients suffering from neurogenic lower urinary tract dysfunction (NLUTD) were included into this randomized controlled double-blind trial. At the end of standard urodynamic investigation, the patients received 2 fillings of the bladder using a 4°C (ice water test, IWT) or 36°C (warm water test, WWT) saline solution with a speed of 100 mL/min. The order was randomly selected and patients and investigators were blinded for the order sequence. Primary outcome measure was the occurrence of detrusor overactivity, maximum detrusor pressure and maximum bladder filling volume during IWT and WWT. RESULTS: 40 patients (9 women, 31 men) where used for data analysis. NLUTD was caused by spinal cord injury in 33 and by other neurological disorders in 7 patients. Detrusor overactivity occurred significantly (p=0.02) more often during the IWT (30/40, 75%) than during the WWT (25/40, 63%), irrespective of the order of the test. Comparing IWT versus WWT, the maximum detrusor pressure was significantly (p<0.001) higher and the maximum bladder filling volume significantly (p<0.001) lower during the IWT. The order of performing the test (IWT first versus WWT first) had no effect on the parameters. CONCLUSIONS: Our findings imply that the more frequent occurrence of detrusor overactivity, higher maximum detrusor pressure and lower bladder filling volume in the IWT compared to the WWT are caused by cold water, underlying the theory of a C-fiber mediated bladder cooling reflex in humans.

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Detrusor contraction during rapid bladder filling: Caused by cold or warm water? A randomized controlled double-blind trial

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Running head: Neurogenic lower urinary tract dysfunction and ice water test

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Abstract

Purpose: We investigated if the detrusor contraction during rapid bladder filling is provoked by cold or warm water.

Patients & Methods: Patients suffering from neurogenic lower urinary tract dysfunction (NLUTD) were included into this randomized controlled double-blind trial. At the end of standard urodynamic investigation, the patients received 2 fillings of the bladder using a 4℃ (ice water test, IWT) or 36℃ (warm water test, WWT) saline solution with a speed of 100 mL/min. The order was randomly selected and patients and investigators were blinded for the order sequence. Primary outcome measure was the occurrence of detrusor overactivity, maximum detrusor pressure and maximum bladder filling volume during IWT and WWT.

Results: 40 patients (9 women, 31 men) where used for data analysis. NLUTD was caused by spinal cord injury in 33 and by other neurological disorders in 7 patients. Detrusor overactivity occurred significantly ($p=0.02$) more often during the IWT (30/40, 75%) than during the WWT (25/40, 63%), irrespective of the order of the test. Comparing IWT versus WWT, the maximum detrusor pressure was significantly ($p<0.001$) higher and the maximum bladder filling volume significantly ($p<0.001$) lower during the IWT. The order of performing the test (IWT first versus WWT first) had no effect on the parameters.

Conclusions: Our findings imply that the more frequent occurrence of detrusor overactivity, higher maximum detrusor pressure and lower bladder filling volume in the IWT compared to the WWT are caused by cold water, underlying the theory of a C-fiber mediated bladder cooling reflex in humans.

Introduction

The ice water test (IWT) was first described 1957 by Bors and Blinn[1] in patients with spinal cord injury (SCI) to differentiate between upper (positive IWT) and lower (negative IWT) motoneuron lesion. However, subsequent studies found that the IWT is not specific to lesions of the upper motoneuron since also non-neurological patients showed a positive IWT and not all patients with an upper motoneuron condition had a positive IWT.[2, 3, 4]

Animal studies in cats showed that the IWT is a C-fiber mediated lower motoneuron segmental reflex and that these unmyelinated C-fibers are associated with cold receptors in the bladder.[5, 6, 7] In healthy humans, the IWT is positive up to the age of about 4 years[8, 9] and becomes negative thereafter since the bladder cooling reflex is centrally inhibited. This reflex, however, might be unmasked by neurological disorders such as cerebrovascular accident, multiple sclerosis, Parkinson's disease, SCI, spina bifida and others.[8]

Considering that C-fibers are involved in the pathogenesis of detrusor overactivity, the IWT is an important diagnostic tool, especially in patients with an underlying neurological disorder.[2, 10] Although there are many studies on the IWT,[2] it is unclear whether the detrusor contraction during rapid bladder filling is provoked by cold or warm water. We therefore designed this randomized controlled double-blind trial.

Patients and Methods

Patients

Potential trial participants were recruited between October 2012 and March 2013 from patients undergoing neuro-urological assessment[11] at the Spinal Cord Injury Center, Balgrist University Hospital, Zürich, Switzerland. Study inclusion criteria were patients with neurogenic lower urinary tract dysfunction (NLUTD) aged ≥18 years. Pregnant and breast feeding women, patients aged <18 years, patients with current urinary tract infection and those who underwent intradetrusor onabotulinumtoxinA injections within the year before evaluation were excluded.

The study was approved by the local ethics committee and registered with ClinicalTrials.gov (NCT identifier: NCT01773213). All subjects provided written informed consent prior to study inclusion.

Randomization and blinding

Patients were randomly assigned to undergo rapid bladder filling after standard urodynamic investigation (UDI) either first with cold water (IWT) and second with warm (warm water test, WWT) water or first with warm and second with cold water. Allocation was done on an equal basis (1:1) using independent random numbers generated by an internet service (random.org). Fluid packing for IWT and WWT looked identical and both patients and investigator (MK, an experience consultant in neuro-urology) involved in data analysis were blinded not being able to conclude on the test sequence. Randomization, fluid preparation and UDI were performed by the same staff nurse not involved in data analysis.

UDI, IWT and WWT

UDIs were done in accordance to good urodynamic practices recommended by the International Continence Society.[12, 13] Patients were urodynamically investigated in a sitting position whenever possible. A multichannel urodynamic system (Sedia®, Givisiez, Switzerland) was applied for all measurements. Pelvic floor electromyographical data were recorded via two perineal surface electrodes. Filling sensations were documented when applicable. Standard UDI was performed using 36℃ saline with a filling speed of 20-30 mL/min. P atients underwent two fast filling cystometries (IWT and WWT) after standard UDI according to our previous study.[14] The IWT was conducted with 4℃ and the WWT with 36° C saline with a filling speed of 100 mL/min upon the occurrence of a detrusor contraction or upon a maximum bladder filling volume of 500 mL.

Outcome measures

Primary outcome measures were the occurrence of detrusor overactivity (yes/no), maximum detrusor pressure (cmH_2O) and maximum bladder filling volume (mL) during IWT and WWT.

Secondary outcome measures were sensations (no sensation or sensation of cold, urgency and pain), urinary incontinence (yes/no) and maximum heart rate (beats per minute) during IWT and WWT.

Tertiary outcome measures were occurrence of adverse events during the study period.

Statistical analyses

To detect a difference of 10 cmH_2O in maximum detrusor pressure comparing IWT and WWT with a two-tailed t-test for paired samples at a significance level of 5% (α=0.05) and a statistical power of 80% (β=0.2) assuming a standard deviation of difference in the response of matched pairs of 20 cmH_2O, we would have to include 34 patients. Expecting a drop out rate of 10%, we decided to recruit at least 38 patients.

The effect of the order of IWT and WWT on occurrence of detrusor overactivity, maximum detrusor pressure, maximum bladder filling volume and maximum heart rate was analyzed using an ANOVA for repeated measures with within factor “temperature” (cold versus warm) and between factor “order” (cold first versus warm first). For this analysis, maximum detrusor pressure was logarithmically transformed (log10 of maximum detrusor pressure in cmH_2O plus 1).

To compare secondary outcome measures between IWT versus WWT, to investigate an order effect, and to compare the occurrence of detrusor overactivity during the standard UDI and the WWT, the the McNemar and the Fisher’s exact test were used. Statistical analyses were performed applying IBM® SPSS® Statistics version 23 (IBM® Armonk, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 50 patients were assessed for trial eligibility (figure 1). Of these, 41 gave informed consent and were eventually randomized to IWT first (n=25) or WWT first (n=16). One patient of the IWT first group had to be excluded due to a technical problem leaving a total of 40 patients for analysis.

Of the 40 analyzed patients, mean age was 50 ± 16 years (range 22 to 83), 9 (23%) were women and the cause of NLUTD was SCI in 33 patients (83%), multiple sclerosis in 2 (5%) and other neurological disorders in 5 (spina bifida, cerebral palsy, tethered cord syndrome, chronic inflammatory demyelinating polyneuropathy, herniated disk).

Detrusor overactivity occurred significantly ($p=0.02$) more often during the IWT (30/40, 75%) than during the WWT (25/40, 63%), irrespective of the order of the test. Comparing IWT versus WWT, there was a significantly ($p<0.001$, figure 2) higher mean maximum detrusor pressure and a significantly ($p<0.001$, figure 3) lower mean maximum bladder filling volume during IWT. The order of performing the test (IWT first versus WWT first) showed no significant differences in mean maximum detrusor pressure ($p=0.16$, figure 2) and mean maximum bladder filling volume ($p=0.61$, figure 3). Moreover, no significant ($p>0.05$) differences were found regarding secondary outcome measures, when comparing IWT versus WWT and the order of the test.

A significant ($p=0.006$) difference was found comparing the occurrence of detrusor overactivity during the standard UDI (35/40, 88%) versus during the WWT (25/40, 63%).

No study related adverse events were reported.

Discussion

In the present randomized controlled double-blind trial, we found more frequent occurrence of detrusor overactivity, higher maximum detrusor pressure and lower bladder filling volume in the IWT compared to the WWT. This implies that our results are caused by cold water, which is in line with the findings of several other non-randomized studies, underlying the theory of a C-fiber mediated bladder cooling reflex in humans.[2, 10]

The IWT is positive upon the age of about four years and becomes negative thereafter, since by growth the inhibiting signals from the central nervous system increase and the C-fiber reflex is suppressed.[9] In the case of a disorder of the central nervous systems (for instance alterations in neural control such as in patients with SCI), the C-fiber reflex can often not be suppressed and the IWT becomes positive again.[9] C-fiber mechanosensitivity might also change in response to chemical or thermal stimuli.[10, 15]. Classically, the IWT is used to differentiate between upper (positive IWT) and lower (negative IWT) motoneuron lesion.[1, 2, 3, 4] However, a positive IWT in a significant percentage of patients with other urological conditions might indicate emerging C-fiber function compared to that in normal individuals in whom C-fibers are dormant.[2]

Hellstroem et al.[16] detected different types of detrusor contraction after cold water instillation compared to standard UDI and therefore assumed that the cold receptors shown in animal experiments are also present in the human urinary bladder. In agreement with our findings in humans, Fall et al.[6] showed in animal experiments that detrusor contractions started earlier in the IWT compared to bladder filling with warm water. Using stepwise nerve transections, they revealed that the bladder is mediated by unmyelinated C-fibers originating from cold receptors in the bladder and the urethra.[6] Moreover, the detrusor pressure in cats increased by reducing the temperature of the infused saline keeping the infusion speed unchanged.[6] These results are in line with the report by Geirsson et al.[8] and also our findings.

In animals, the micturition reflex seems A-delta mechanoreceptor driven with a higher threshold volume compared to the C-fiber mediated bladder cooling reflex.[17, 18, 19] Cold water may decrease the threshold volume leading to a reflex discharge in bladder preganglionic neurons.[17, 18, 19]. In addition, the bladder cooling reflex can be activated without any background activity of A-delta-fiber mediated mechanoreceptors of the bladder wall.[7] Mainly based on animal research, it is generally assumed that A-delta fibers are essential for the initiation of the micturition reflex and that C-fibers primarily respond to noxious chemical and mechanical stimuli.[20] The main findings of our randomized controlled trials, i.e. more frequent occurrence of detrusor overactivity, higher maximum detrusor pressure and lower bladder filling volume in the IWT compared to the WWT, further support this hypothesis and imply that in humans with NLUTD C-fibers become activated and facilitate pathological reflexes triggered by noxious stimuli such as cold water.

Another relevant issue with the IWT is that the methods how to perform this test vary widely between the different studies.[2] We used the same criteria for the IWT as Geirsson et al.[10] but with a maximum bladder infusion volume of 500 mL to prevent false negative results by stopping the IWT too early. Although the IWT is recognized as a possible diagnostic tool to discriminate between an upper and lower moto-neuron lesion by the European Association of Urology (EAU) Guideline on Neuro-Urology,[21] there is no generally agreed algorithm how to use this test in daily clinical practice and also the widely used guidelines/recommendations of the American

Urological Association (AUA),[22] the EAU,[21] the International Consultation on Incontinence (ICI),[23] and the International Continence Society (ICS)[12, 24] are not very instructive. Thus, standardization of the IWT is mandatory to compare results, determine specificity and sensitivity and define normative values to establish clinically relevant nomograms. Based on the literature[2, 14] and our own findings, we recommend to perform the IWT using 4°C saline with a filling speed of 100 mL/min upon the occurrence of a detrusor contraction, urinary leakage, autonomic dysreflexia, or pain or upon a maximum bladder filling volume of 500 mL.

Although we compared to the best of our knowledge for the first time urodynamic parameters of the IWT and WWT randomly and in a double-blind manner, our study has limitations. It should be considered that our unit is part of a highly specialized university spinal cord injury center so that a selection bias by inclusion of more severe cases, mixed population and/or unbalanced gender distribution cannot be completely excluded. Moreover, most of our patients were men and suffered from SCI but the limited total number of included patients did not allow for sub-group analysis. In addition, although we did find a significant difference between standard UDI and the WWT regarding the occurrence of detrusor overactivity, no definitive conclusions can be drawn regarding a potential effect of the filling speed since we did not randomize slow versus fast filling. However, it should be considered that a slow bladder filling with cold water would cause interpretation difficulties due to the heating-up of the cold water during the slow filling phase.

Conclusions

The findings of our randomized controlled double-blind trial imply that the more frequent occurrence of detrusor overactivity, higher maximum detrusor pressure and lower bladder filling volume in the IWT compared to the WWT are caused by cold water, underlying the theory of a C-fiber mediated bladder cooling reflex in humans.

Acknowledgement

None of the authors has a conflict of interest related to the submitted work.

Conflict of interest statement

This study was funded by the Swiss Continence Foundation (www.swisscontinencefoundation.ch), which had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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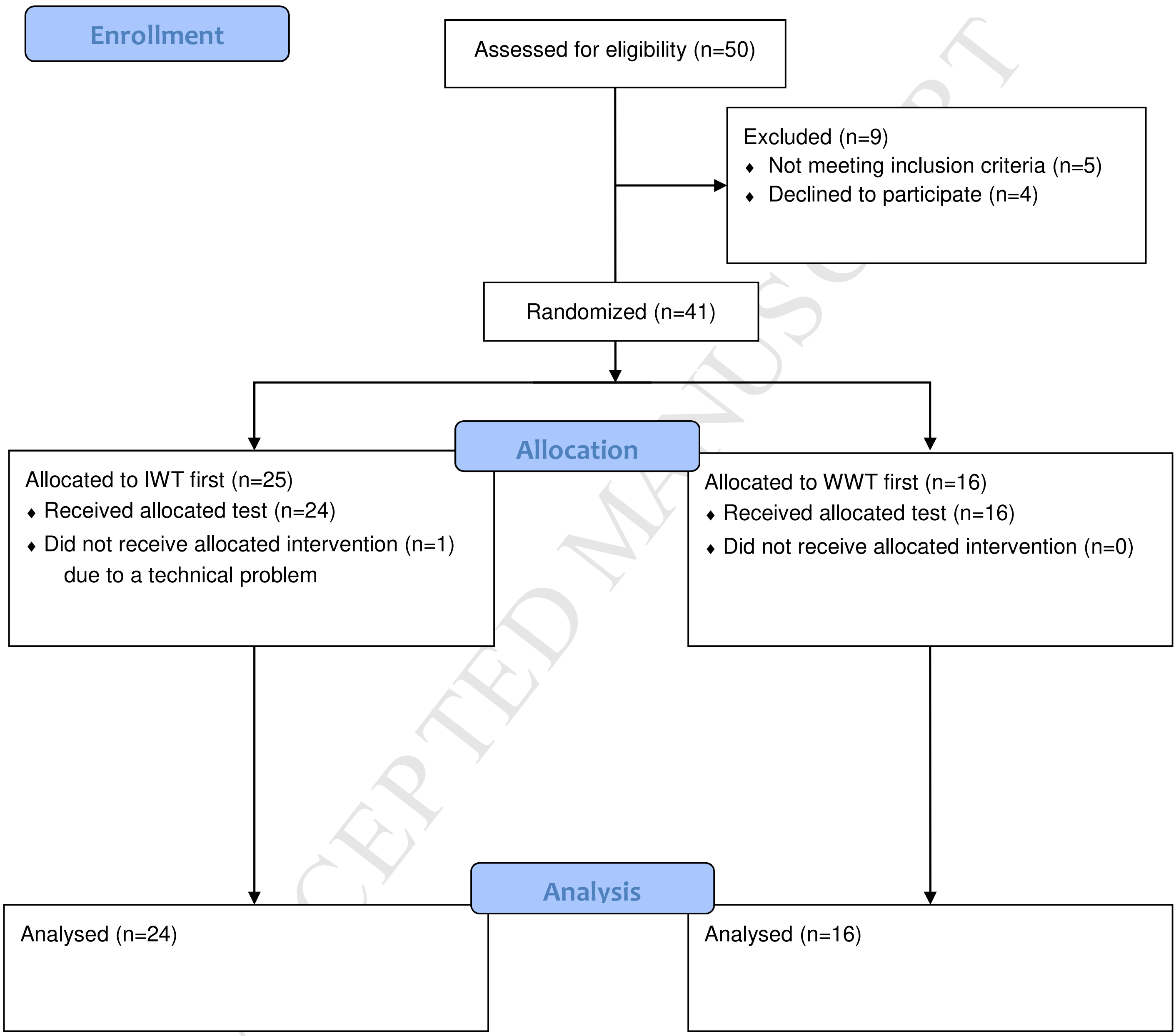

Figure 1. CONSORT flow diagram

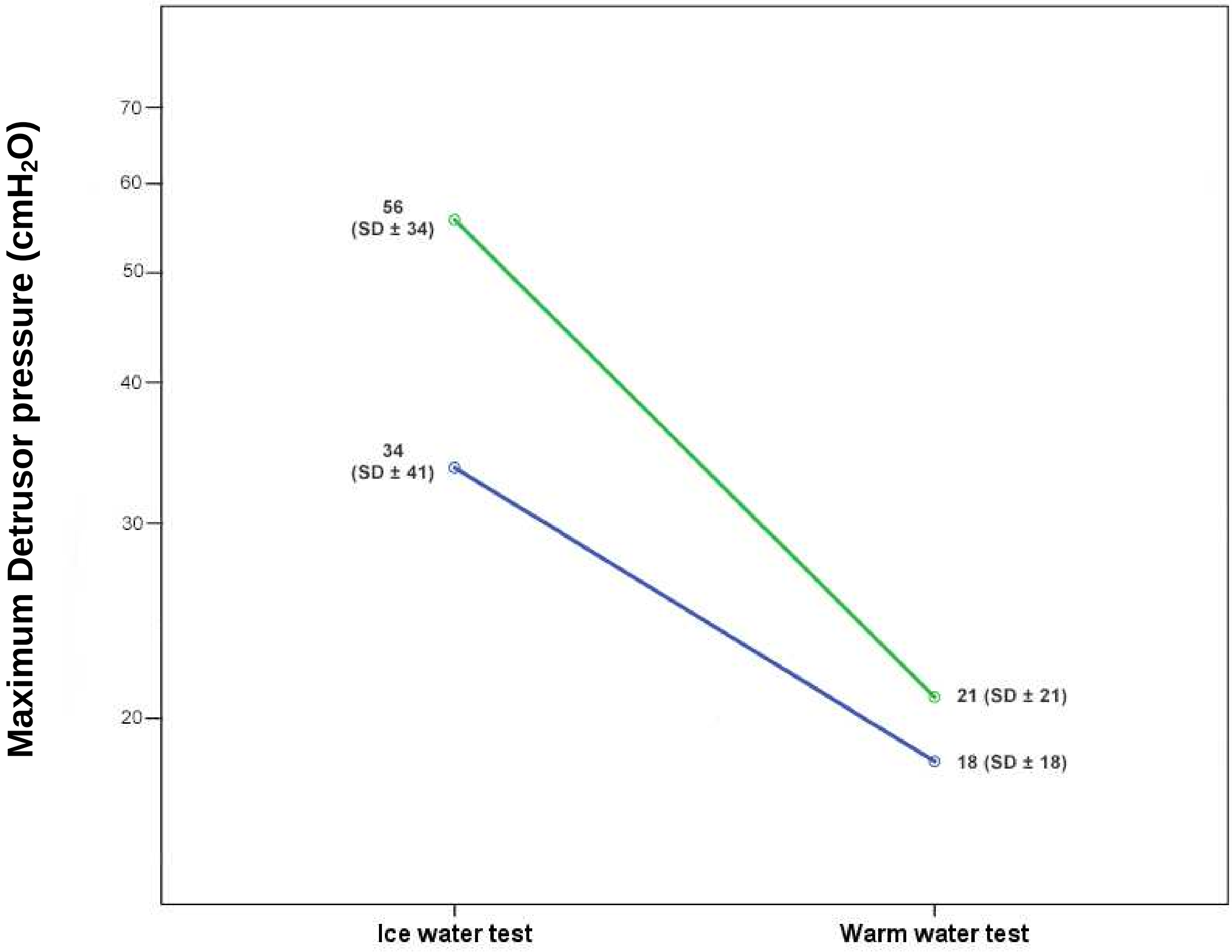

Figure 2. Detrusor pressure (cmH_2O) during the ice and warm water test (IWT, WWT). The mean maximum detrusor pressure was significantly ($p<0.001$) higher in the IWT compared to the WWT (n=40). The order of performing the test (IWT first versus WWT first) showed no significant ($p>0.05$) differences in mean maximum detrusor pressure. **–** (**green**) IWT first, WWT second (n=24), **– (blue)** WWT first, IWT second (n=16). SD = standard deviation.

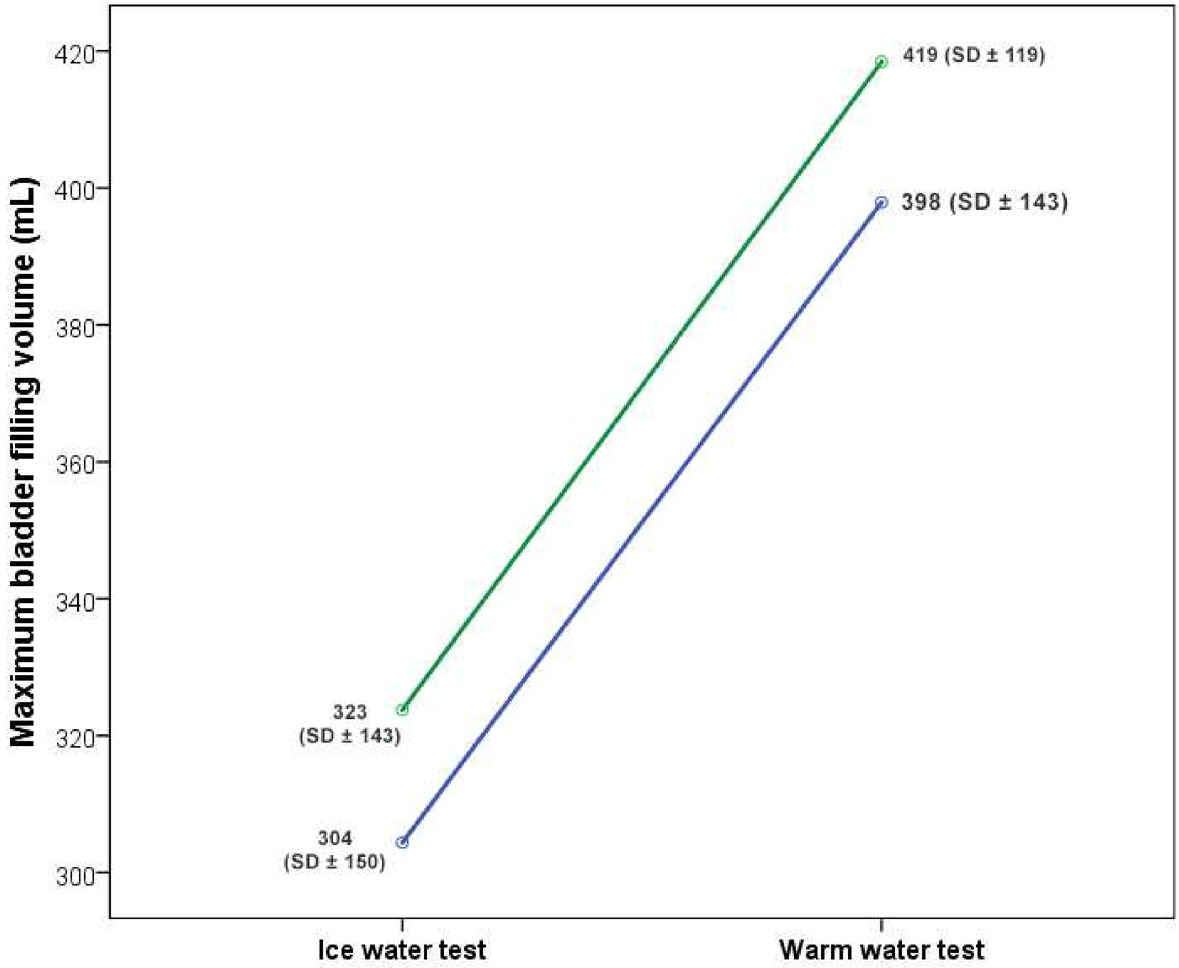

Figure 3. Bladder filling volume (mL) during the ice and warm water test (IWT, WWT). The mean maximum bladder filling volume was significantly ($p<0.001$) lower in the IWT compared to the WWT (n=40). The order of performing the test (IWT first versus WWT first) showed no significant ($p=0.61$) differences in mean maximum bladder filling volume. **–** (**green**) IWT first, WWT second (n=24), **–** (**blue**) WWT first, IWT second (n=16). SD = standard deviation.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4 - 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4 - 5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4 - 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	5 / 4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Key of Definition

NLUTD	= neurogenic lower urinary tract dysfunction
IWT	= ice water test
SCI	= spinal cord injury
UDI	= urodynamic investigation
WWT	= warm water test